Oxygen therapy is important in the treatment of several acute and chronic cardiorespiratory disorders associated with hypoxemia. Administration of oxygen reduces pulmonary arterial pressure by correcting hypoxemia [1], and symptomatically improves breathlessness either during exercise or at rest [2]. In patients with chronic obstructive pulmonary disease (COPD), high concentrations of inspired oxygen may result in
hypercapnia [3, 4]. It is generally believed that this is due to a loss of the hypoxic drive with consequent diminished total minute ventilation (MV) and a concomitant rise in arterial CO₂ tension (PaCO₂) [5]. This oxygen suppression is especially problematic when CO₂ retention has already increased the buffering capacity of blood and thus limits the change in the central chemoreceptor pH that would otherwise be compensatory [6]. In this circumstance, one would expect that patients with hyperoxia-induced hypercapnia might have a blunted hypercapnic drive and an intact hypoxic drive, and that patients who do not develop hyperoxia-induced hypercapnia might have an intact hypercapnic drive. However, hypoventilation and a diminished respiratory drive are seldom identified and treated before oxygen therapy is given to patients with chronic stable hypoxemic COPD.

The mouth occlusion pressure 0.1 second after the onset of inspiration (P₀.₁) represents the neuromuscular component in response to the central respiratory output in normal subjects and patients with lung disease [7]. A previous study showed that the central respiratory output is abnormal in hypercapnic COPD patients, with a decrease in P₀.₁ and the P₀.₁ change in response to CO₂ challenge (P₀.₁CO₂) [8]. Thus, it is possible that oxygen therapy may place these patients at further risk of hypercapnia by blunting central respiratory output. However, it is not known whether oxygen therapy blunts the hypoxic respiratory drive alone or aggravates an impaired hypercapnic respiratory drive.

The purpose of this investigation was to evaluate the magnitude of chemoresponsiveness assessed in terms of P₀.₁, P₀.₁CO₂, MV response to CO₂ stimulation (MVCO₂), and blood gas tension after low flow oxygen supplementation in COPD patients.

Materials and Methods

Subjects
Ambulatory outpatients with COPD who met the diagnostic criteria of the American Thoracic Society (ATS) guidelines [9], and who were clinically and functionally stable for at least 2 months prior to the study, were enrolled. To evaluate the severity of COPD and its effect on chemoresponsiveness to oxygen therapy, subjects were divided into two groups: normocapnic and hypercapnic patients. Patients maintained their regular regimen and dosage of bronchodilators and/or steroids, but refrained from using bronchodilators 8 to 10 hours before the study. All patients were asked not to drink coffee or tea on the morning of the study day. No patients were taking any sedatives, tranquilizers, opiate-containing drugs, or medication that may have influenced consciousness or the respiratory center. Informed consent was obtained from each subject prior to enrollment.

Protocol
Pulmonary function was measured 1 week before the study. Forced vital capacity (FVC), forced expiratory volume in 1 second (FEV₁), FEV₁/FVC, and functional residual capacity were measured using a body plethysmograph (System 6200; Sensor Medics, Yorba Linda, CA, USA). Each subject sequentially received room air and then oxygen at 2 L/minute through a nasal cannula for 1 hour. Arterial oxygen saturation (SaO₂) was monitored throughout the study using pulse oximetry (Model 3301; BCI International Co, Waukesha, WI, USA). To study whether the improvement in hypoxemia or alveolar ventilation altered the respiratory drive response, arterial blood gas (Corning 278 Blood Gas Analyzer, Ciba-Corning Diagnostics Co, Medfield, MA, USA), P₀.₁, maximum inspiratory mouth pressure (PImax), and MV were measured with room air and immediately after oxygen therapy. Oxygen supplementation may result in hypercapnia in COPD patients [3, 4]. To clarify whether the respiratory drive response to CO₂ stimulation was blunted in normocapnic or hypercapnic COPD patients, 6% CO₂ was inspired and P₀.₁CO₂ and MVCO₂ were subsequently measured before and after oxygen therapy. When the end tidal CO₂ pressure (PₚₕCO₂) increased more than 10 mmHg from baseline after 6% CO₂ inspiration, the P₀.₁ measurement was repeated.

Measurement of P₀.₁, MV, and PImax
Patients were comfortably seated wearing a nose clip and with the mouthpiece of a pneumotach apparatus with an electronically controlled magnetic shutter valve (MS PFT; Erich Jaeger, Hoechberg, Germany). The shutter was activated at end-expiration at irregular intervals during measurement. At the end of expiration, the shutter was set automatically. After 0.1 seconds, P₀.₁ was measured while the patient attempted to inhale and expressed in kPa. The trial was ended after the shutter was set about 10 to 15 times. The pneumotach apparatus was also used to measure MV. The values used for P₀.₁ and MV were obtained from the mean of the last 10 breaths.

PImax was measured with the patient exerting maximal inspiratory effort. As soon as the patient started to inhale, the shutter closed and the pressure was measured automatically. Measurement of PImax was performed using a one-way non-rebreathing method. Maneuvers were repeated until three measurements with less than 5% variability were recorded. The highest value obtained was used in the analysis.
CO₂ challenge test

P₀.₁CO₂ was measured while the patient inhaled 6% CO₂ gas mixture (6% CO₂, 94% room air) from a cylinder though a 25-L rebreathing bag, which was connected to a Y-valve (Erich Jaeger, Hoechberg, Germany) with a shutter. The patient was asked to approach the mouthpiece and to breathe quite normally from the gas bag for 1 to 3 minutes, allowing the patient to equilibrate with the circuit as shown by the plateau on the Pₑ₇₀CO₂ record. P₀.₁CO₂ was the value when the Pₑ₇₀CO₂ was 10 mmHg above base data. The slope was calculated as P₀.₁CO₂ - P₀.₁/ increase in Pₑ₇₀CO₂ over baseline (~10 mmHg), expressed as ΔP₀.₁/Pₑ₇₀CO₂. Pₑ₇₀CO₂ was measured continuously at the mouth using an infrared CO₂ meter (Capnometer 8200; BCI International Co). SaO₂ was continuously monitored using a pulse oximeter (3301; BCI International Co). arterial blood gases, respiratory drive, MV and PImax were determined by unpaired t-test. The physiologic change in arterial blood gas, respiratory drive, MV and PImax after oxygen supplementation or CO₂ challenge in each group was compared by the paired t-test. The correlation of FVC or FEV₁ and ΔP₀.₁/Pₑ₇₀CO₂ or MVCO₂, ΔP₀.₁/Pₑ₇₀CO₂ and MVCO₂, ΔP₀.₁/Pₑ₇₀CO₂ and PaCO₂ were determined using Pearson’s test. Statistical significance was considered as a p value less than 0.05.

Results

Twenty-six ambulatory outpatients with COPD were enrolled in this study. Fourteen patients were normocapnic (PaCO₂ < 45 mmHg) with mild airway obstruction (FEV₁, 66.6 ± 4.5% of predicted value; FEV₁/FVC, 60.6 ± 3.9%) and 12 patients were hypercapnic (PaCO₂ ≥ 45 mmHg) with moderately severe airway obstruction (FEV₁, 31.4 ± 2.3% of predicted value; FEV₁/FVC, 48.1 ± 3.1%) (Table 1). Hypercapnic patients showed a significantly lower FVC (1.6 ± 0.1 L, p < 0.0001) and FEV₁ (0.7 ± 0.3 L, p < 0.0001) than normocapnic patients (FVC, 2.7 ± 0.2 L; FEV₁, 1.6 ± 0.1 L). There was a significant increase in hyperinflation in the hypercapnic group (residual volume, RV/total lung capacity, TLC, 76.1 ± 2.1%) compared to the normocapnic group (RV/TLC, 50.5 ± 1.1%, p < 0.0001) (Table 1).

As shown in Table 2, arterial oxygen tension (PaO₂) was significantly lower in the hypercapnic group than in the normocapnic group (p < 0.001). Arterial pH was similar in both groups, but bicarbonate content was higher in the hypercapnic group. PaO₂, oxygen saturation, and PaCO₂ were significantly increased in COPD patients with or without hypercapnia (all p < 0.01) after oxygen therapy. Arterial pH did not change significantly after oxygen therapy in either group.

P₀.₁ response to oxygen supplementation

Hypercapnic patients had a significantly higher P₀.₁ (0.7 ± 0.07 kPa) than normocapnic patients (0.3 ± 0.03 kPa, p < 0.01) (Fig. 1). In hypercapnic patients, P₀.₁ was significantly reduced to 0.6 ± 0.09 kPa (p < 0.05) with supplemental oxygen. However, there was no suppression of P₀.₁ in normocapnic patients after oxygen therapy. P₀.₁ significantly increased in response to CO₂ challenge in both normocapnic and hypercapnic patients (Fig. 2). The increase in P₀.₁ in normocapnic COPD patients (129.1 ± 25.5%) was significantly greater than that in hypercapnic patients (47.3 ± 8.7%, p < 0.01). With oxygen therapy, P₀.₁ was significantly elevated in response to CO₂ challenge in both normocapnic and hypercapnic patients (Fig. 2).

Table 1. Demographic characteristics and pulmonary function of chronic obstructive pulmonary disease (COPD) patients with normocapnia and chronic hypercapnia

<table>
<thead>
<tr>
<th></th>
<th>Normocapnic COPD</th>
<th>Hypercapnic COPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>14</td>
<td>12</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>59.4 ± 2.2</td>
<td>63.8 ± 2.9</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>11/3</td>
<td>10/2</td>
</tr>
<tr>
<td>FVC (L)</td>
<td>2.7 ± 0.2</td>
<td>1.6 ± 0.1†</td>
</tr>
<tr>
<td>FVC (% pred)</td>
<td>91.6 ± 5.5</td>
<td>54.1 ± 5.0†</td>
</tr>
<tr>
<td>FEV₁ (L)</td>
<td>1.6 ± 0.1</td>
<td>0.7 ± 0.03†</td>
</tr>
<tr>
<td>FEV₁ (% pred)</td>
<td>66.6 ± 4.5</td>
<td>31.4 ± 2.3†</td>
</tr>
<tr>
<td>FEV₁/FVC</td>
<td>60.6 ± 3.3</td>
<td>48.1 ± 3.1*</td>
</tr>
<tr>
<td>TLC (L)</td>
<td>5.5 ± 0.4</td>
<td>6.5 ± 0.7</td>
</tr>
<tr>
<td>TLC (% pred)</td>
<td>112.0 ± 6.2</td>
<td>141.3 ± 12.7*</td>
</tr>
<tr>
<td>RV/TLC (%)</td>
<td>50.5 ± 1.1</td>
<td>76.1 ± 2.1†</td>
</tr>
<tr>
<td>DLCO (mL/min/mmHg)</td>
<td>17.2 ± 1.5</td>
<td>6.7 ± 0.8†</td>
</tr>
<tr>
<td>DLCO (%)</td>
<td>95.6 ± 6.7</td>
<td>43.8 ± 7.0†</td>
</tr>
<tr>
<td>PaCO₂ (mmHg)</td>
<td>36.5 ± 1.3</td>
<td>53.1 ± 1.7†</td>
</tr>
<tr>
<td>PaO₂ (mmHg)</td>
<td>82.5 ± 2.3</td>
<td>53.0 ± 4.4†</td>
</tr>
</tbody>
</table>

M = male; F = female; FVC = forced vital capacity; FEV₁ = forced expiratory volume in 1 second; TLC = total lung capacity; RV = residual volume; DLCO = diffusion capacity measured by single breath method; pred = predicted value. *p < 0.05, †p < 0.0001 compared to the normocapnic COPD group.
However, the increase was significantly smaller in hypercapnic patients (30.7 ± 6.1%) than in normocapnic patients (98.3 ± 22.2%, p < 0.05). In hypercapnic patients, P\textsubscript{0.1}/P\textsubscript{ETCO\textsubscript{2}} in response to CO\textsubscript{2} challenge was significantly depressed from 0.2 ± 0.05 to 0.1 ± 0.03 (p < 0.05) with supplemental oxygen (Fig. 3). There was no significant change in P\textsubscript{0.1}/P\textsubscript{ETCO\textsubscript{2}} in normocapnic patients.

### Ventilation response to oxygen supplementation

P\textsubscript{Imax} in hypercapnic patients (3.9 ± 0.3 kPa) was significantly decreased compared to that in normocapnic patients (5.5 ± 0.4 kPa, p < 0.01). MV was slightly higher in normocapnic patients and did not show any change after oxygen therapy. In contrast, MV\textsubscript{CO2} significantly increased in both groups when subjects inspired either room air or oxygen (both p < 0.01) (Table 3). The percentage increase in MV\textsubscript{CO2} was significantly higher in normocapnic patients (room air, 73.4 ± 12.3%; oxygen therapy, 93.1 ± 13.8%) than in hypercapnic patients (room air, 32.3 ± 7.2%, p < 0.05; oxygen therapy, 13.0 ± 2.8%, p < 0.001, Fig. 4). With oxygen therapy, the percentage increase in MV\textsubscript{CO2} in hypercapnic patients was lower (p < 0.05) (Fig. 4). Furthermore, MV\textsubscript{CO2} was significantly correlated to P\textsubscript{0.1}/P\textsubscript{ETCO2} (r = 0.68, p < 0.0001) (Fig. 5), but not related to baseline P\textsubscript{0.1}. There was good correlation between MV\textsubscript{CO2} and both FVC (r = 0.62, p < 0.001) and FEV\textsubscript{1} (r = 0.70, p < 0.0001), and between P\textsubscript{0.1}/P\textsubscript{ETCO2} and both FVC (r = 0.41, p < 0.05) and FEV\textsubscript{1} (r = 0.45, p < 0.05) (Fig. 6). In addition, PaCO\textsubscript{2} was inversely related to P\textsubscript{0.1}/P\textsubscript{ETCO2} (r = -0.57, p < 0.01) (Fig. 7).

### Discussion

In this study of short-term oxygen therapy in clinically stable COPD patients with hypercapnia, arterial pH was maintained within normal limits, suggesting a lower capacity to clear CO\textsubscript{2} in patients who were well compensated that was not due to an acute effect. Our study demonstrated that hypercapnic patients had more severe airway obstruction and air-trapping than normocapnic patients. The higher baseline P\textsubscript{0.1} in hypercapnic patients suggests that a higher resistive load on airways may heighten baseline respiratory drive in these patients [10–13]. In addition, our results showed that oxygen supplementation significantly reduced P\textsubscript{0.1} in hypercapnic patients but not in normocapnic patients, suggesting that the increased baseline P\textsubscript{0.1} was
partially attributable to hypoxemia. After oxygen therapy, an increase in PaO₂ may attenuate hypoxic stimulation in hypercapnic patients who have relatively high central respiratory drives, in turn reducing P₀₁CO₂.

The baseline state of the central controller in COPD has remained controversial. Our results showed that P₀₁ was increased in patients with severe COPD. The respiratory drive maintained a relatively intact response to further increases in CO₂. However, P₀₁/PETCO₂ was higher in normocapnic patients and lower in hypercapnic patients. Altose et al showed that chemosensitivity was impaired only in hypercapnic patients [8]. Moreover, an inherent CO₂ unresponsiveness has been reported in family members of hypercapnic patients [14]. Therefore, CO₂ retention in patients with COPD may be due to an intrinsically blunted response to hypercapnia. Alternatively, it is possible that the respiratory center becomes blunted as CO₂ accumulates and thus decreases the response to oxygen therapy.

Several mechanisms have been proposed to explain the reasons for oxygen therapy-induced hypercapnia in subjects with COPD, including hypoventilation [5, 8, 15], a shift in the distribution of ventilation to areas with high ventilation-perfusion (V/Q) ratios [16], an increase in right to left shunt [7], and the Haldane effect [17]. The last two mechanisms appear to be the least important [18]. Oxygen therapy may increase pulmonary deadspace by reversing preexisting regional vasoconstriction in the lungs which, in turn, increases perfusion through poorly ventilated lung zones, thus diverting blood flow from well-ventilated areas and resulting in an increase in deadspace and PaCO₂ [19–22]. Therefore, the V/Q distribution may be related to the severity of COPD and may contribute to CO₂ retention in COPD patients with severe airway obstruction receiving oxygen therapy, thus worsening the blunted respiratory drive response to CO₂ challenge [7]. However, our study found that both hypercapnic and normocapnic COPD patients responded to CO₂.

### Fig. 2. Individual mouth occlusion pressure (P₀₁) in A) normocapnic chronic obstructive pulmonary disease (COPD) patients and B) hypercapnic COPD patients in response to CO₂ challenge. Receiving room air (○); supplemental oxygen (●). *p < 0.001 compared to corresponding groups without CO₂ challenge.

### Table 3. Maximum inspiratory pressure (PImax) and minute ventilation (MV) in patients with chronic obstructive pulmonary disease (COPD)

<table>
<thead>
<tr>
<th></th>
<th>Normocapnic COPD (n = 14)</th>
<th>Hypercapnic COPD (n = 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Room air</td>
<td>O₂ 2 L/min</td>
</tr>
<tr>
<td>PImax (kPa)</td>
<td>5.5 ± 0.4</td>
<td>5.6 ± 0.4</td>
</tr>
<tr>
<td>PImax%</td>
<td>52.1 ± 3.7</td>
<td>52.9 ± 4.5</td>
</tr>
<tr>
<td>MV (L/min)</td>
<td>15.4 ± 0.9</td>
<td>13.7 ± 0.9</td>
</tr>
<tr>
<td>MVCO₂ (L/min)</td>
<td>26.4 ± 2.1*</td>
<td>25.8 ± 2.3*</td>
</tr>
</tbody>
</table>

P₀₁ = mouth occlusion pressure 100 msec after the beginning of inspiration; PImax% = percentage of predicted PImax; MVCO₂ = MV with 6%CO₂. *p < 0.01 compared to normocapnic COPD without O₂ therapy; †p < 0.001. ‡p < 0.01 compared to MV of corresponding group breathing room air or oxygen; \*p < 0.01 compared to MVCO₂ with room air in hypercapnic patients.
challenge, indicating that baseline chemoresponsiveness to elevated levels of CO₂ was preserved. With oxygen supplementation, MV and the change in MVCO₂ were significantly reduced in hypercapnic patients. In contrast, MVCO₂ in normocapnic patients was not significantly altered with oxygen supplementation. The blunted response of MV to elevated PaCO₂ was also reflected by a decrease in the change in P₀.₁/CO₂. Our results indicated that chemoresponsiveness to elevated PaCO₂ was not impaired at baseline in COPD patients, but became blunt with oxygen therapy in patients with chronic hypercapnia. Therefore, even low-concentration oxygen therapy used to improve hypoxemia may decrease the chemoresponsiveness to elevated PaCO₂ in hypercapnic patients, placing them in jeopardy of an impaired ventilatory response in combating severe respiratory distress.

Patients with chronic hypercapnic COPD have an excessive load on the inspiratory muscles in relation to their maximal strength [23, 24], contributing to an increased level of P₀.₁. Using needle electrodes inserted in the diaphragm, De Troyer et al documented an increased neural drive in severe COPD patients [25]. In patients with COPD and hypercapnia, the neural inspiratory drive is relatively preserved. In contrast, patients with severe COPD reach peak values of neuromuscular inspiratory drive and no further increment in the P₀.₁ can be expected to maintain PaCO₂ within the normal range. Sorli et al reported that patients with hypercapnia seemed to have a decreased neuromuscular inspiratory drive in relation to the observed increment in PaCO₂ [14]. The body adapts to chronic hypercapnia by reducing the sensitivity to CO₂. This hypothesis is further supported by the lower FVC, FEV₁, MVCO₂ and ΔP₀.₁/PE₀.₂ seen in our hypercapnic patients.

In this study, we chose low flow oxygen therapy at 2 L/minute, which is conventional in the treatment of hypoxemia at rest or during exercise to increase exercise capacity or relieve the symptoms/signs of cor pulmonale [2, 26]. In contrast to a previous study using extremely high oxygen concentrations [18], this study
may reflect the impact of oxygen use in common clinical practice on ventilatory response in COPD patients. Oxygen supplementation increased PaCO₂ in both normocapnic and hypercapnic COPD patients. This may have been due to the slight decrease in MV after oxygen supplementation. However, the increase in PaCO₂ did not influence the arterial pH.

The interaction between resting P₀.₁, MV, and P₀.₁CO₂ in COPD patients remains unclear. Previous studies demonstrated that the resting respiratory drive as expressed by P₀.₁ is increased in both normocapnic and hypercapnic COPD patients [11–13]. In contrast, Altose et al demonstrated that P₀.₁ is impaired in hypercapnic patients [8]. The high resting MV (13–15 L/min) in our patients may have been related to rapid respiratory frequency and excessive load imposed on the inspiratory muscles as well as elevated P₀.₁. Our results are similar to previous reports [11, 23]. However, other reports demonstrated that a reduction in MV of less than 10 L/minute could allow COPD patients to reduce the pressure required for breathing, thus minimizing respiratory effort and dyspnea, and avoiding fatigue [24, 27, 28]. The discrepancy in resting MV between different studies may be dependent on the severity of airway obstruction in study patients. Other factors such as hyperinflation, an increased physiologic deadspace, and high V/Q mismatch have been reported to contribute to chronic hypercapnia in COPD patients [29].

Since the P₀.₁/PₚₖCO₂ was significantly related to FVC and FEV₁, it is also possible that more severe airflow obstruction in hypercapnic patients may contribute, in part, to inadequate CO₂ elimination capacity after oxygen therapy [11]. However, in this situation, PₚₖCO₂ may be underestimated to represent the actual PaCO₂ in those patients after CO₂ challenge,
and the change in $P_{0.1}\text{CO}_2$ may be lower than $P_{0.1}/P_{ET}\text{CO}_2$, as in this study, indicating that hypercapnic COPD patients are less responsive to elevated $P_{\text{aCO}_2}$ than we estimated. However, the finding that the MVCO$_2$ was not significantly different between normocapnic and hypercapnic patients (Fig. 4) suggests that this may not have been the case in our study.

Studies of ventilatory response to oxygen in patients with COPD have shown variable results. Sassoon et al's report of COPD patients with a supplement of 100% oxygen for 15 minutes found no relationship between hyperoxia-induced hypercapnia and depression of ventilation because of the varying responses [18]. Shonhofer et al showed that oxygen induced hypercapnia in COPD patients with a retainer of CO$_2$ [27]. These inconsistent results may be due to the varying severity of COPD in the study patients.

Although a single CO$_2$ level in steady-state CO$_2$ stimulating test is a more feasible clinical measure for determining $P_{0.1}\text{CO}_2$, it might not be accurate enough to calculate $P_{0.1}/P_{ET}\text{CO}_2$. Changing the concentrations of CO$_2$ (from 1% to 6%) in air breathed during the measurement of occlusion pressure may allow accurate calculation of $P_{0.1}/P_{ET}\text{CO}_2$. In addition, caution should be taken to avoid the effect of hypoxic stimulation on the measurement of $P_{0.1}\text{CO}_2$ when patients inappropriately hyperventilate during inhalation of the 6% CO$_2$ gas mixture. Therefore, the rebreathed gas should also be analyzed to ascertain that the fractional concentration of oxygen in inspired gas remains above 21%. The oxygen saturation may also be monitored by pulse oximeter.

In summary, our study suggests that COPD patients who are vulnerable to suppression of the respiratory drive by oxygen therapy and suppression of MVCO$_2$ are associated with greater air-trapping and hypercapnia.

Clinically, care should be taken in using oxygen therapy in patients with more severe COPD, as they may have a blunted response to acute CO$_2$ retention due to suppression of the respiratory center.

References


